REMARKS

Status of the Application

Claim 1 has been amended. Basis for this amendment can be found as follows: "at least one functional, stable, and autonomous" (mini-chromosome), which is the definition of "adchromosomal," as found on page 65, last two lines to the first four lines of page 66. The phrase "plant centromere comprising a polynucleotide comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs:1, 2, 3, 24, 25, 26, 37, 38, 39, 51, and 52, or a fragment of 20-360 nucleotides of said nucleic acid sequence" enjoys support on page 17, line 31 to page 18, line 3 (SEQ ID NOs:1, 2, 3, 51, 52 (*Brassica oleracea*)); page 18, lines 9-13 (SEQ ID NOs:24, 25, and 26 (*Glycine max*)); and page 143, last paragraph, which extends to the top of page 144, and Table 24 (SEQ ID NOs:37, 38, and 39), also on page 144, as well as page 26, lines 24-25 ("20-360 bps"). "The polynucleotide sequence confers an ability to segregate the minichromosome to daughter cells through cell division" enjoys support on page 66, 2nd full paragraph, first two lines. Applicants amended claim 45 to correct a typographical error, claim 56 to make the claim read more clearly, and claim 66 to incorporate the limitations of claim 67 and to make claim 66 an independent claim. No new matter has been introduced as a result of any of these amendments. Applicants have also cancelled claims 40, 67, 76, 77, and 82-87. Applicants reserve the right to pursue any cancelled subject matter, whether by claim amendment or cancellation, in this or any continuing application.

Applicants' representative apologizes to the Examiner for the typographical error in the listing of the claims filed July 13, 2007, wherein the representative omitted claim 6. Claim 6 has been cancelled.

Claims 1-3, 7, 10, 11, 14-16, 19, 25, 30, 39, 43-46, 54, 56-62, 66, 89, 90, 93, and 96 are pending.

The rejections under 35 USC § 102 should be withdrawn: the claims are novel

The Office is respectfully requested to withdraw the following rejections under 35 USC 102(b) and 102(e) because (1) the rejections are obviated in part by cancellation of claims 40,

67, 76, 77, 82-87), and (2) none of the cited alleged prior art references fairly disclose plants comprising at least one functional, stable, and autonomous mini-chromosome, wherein the mini-chromosome has a transmission efficiency during mitotic division of at least 90%, and wherein the mini-chromosome comprises the recited nucleic acid sequences, or a fragment of 20-360 nucleotides of the recited nucleic acid sequences:

1. The rejection of claims 1-3, 19, 25, 30, 40, 44-46, 54 56-60, 66-67, 76, 82, and 96 in view of U.S. Patent No. 6,156,953 to Preuss and Copenhaver ("Preuss");
2. The rejection of claims 1-3, 7, 10, 11, 14-16, 19, 25, 30, 43-46, 54, 57, 58, 63, 66-67, 76, 77, 82, 83, and 96 in view of U.S. Patent Application Publication No. 20020123053 ("Luo");
3. The rejection of claims 1-3, 7, 10, 11, 15-16, 19, 25, 30, 40, 43-46, 54, 56-58, 63, 66-67, 76, 82, 89, 90, 93, and 96 in view of U.S. Patent No. 7,119,250 to Keith et al. ("Keith").

The rejections under 35 USC § 103 should be withdrawn: the claims are non-obvious

The Office is respectfully requested to withdraw the rejection under 35 USC 103(a) of claims 1-3, 7, 10-11, 14-16, 19, 25, 30, 39-40, 43-46, 54, 56-63, 66, 67, 76, 77, 82, 83, 89, 90, 93, and 96 as being unpatentable over Preuss in view of Luo. Neither Preuss nor Luo, separately or in combination, render the presently amended claims obvious because the references do not fairly teach or suggest plants comprising at least one functional, stable, and autonomous mini-chromosome, wherein the mini-chromosome has a transmission efficiency during mitotic division of at least 90%, and wherein the mini-chromosome comprises the recited nucleic acid sequences, or a fragment of 20-360 nucleotides of the recited nucleic acid sequences.

The rejection under 35 USC § 112, first paragraph for lack of enablement should be withdrawn

Applicants respectfully request that the Office withdraw its rejection of all pending claims under 35 USC §112, first paragraph, for allegedly being non-enabled: the specification's

teachings clearly enable one skilled in the art to make and use the claimed invention commensurate with the scope of the amended claims. The Office asserted that the specification enables one of skill in the art to make and use only specific minichromosomes with defined sequence content based on species-specific centromere repeats. The Office also averred that the specification fails to provide guidance to enable one to make and use any minichromosome of any size with any DNA content from any species of any kingdom as broadly claimed. The Office seemingly has engaged in a *Wands* analysis, averring that the specification does not provide any guidance for: (1) any minichromosome with any DNA composition as broadly claimed; (2) indicating which sequences are absolutely required for centromere function, telomere function, or origin of replication. The Office also asserts that the function of a centromeric region is unpredictable. Applicants respectfully traverse.

Before discussing the rejection further, Applicants note that they have amended claim 1 (from which all the rejected claims ultimately depend) to include a limitation of reciting specific nucleic acid sequences, and functional derivatives and variants thereof: "comprising at least one functional, stable, and autonomous mini-chromosome, wherein the mini-chromosome has a transmission efficiency during mitotic division of at least 90%, and wherein the mini-chromosome comprises the recited nucleic acid sequences, or a fragment of 20-360 nucleotides of the recited nucleic acid sequences."

The MPEP provides guidance on a proper *Wands* analysis. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue.' These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure" (*MPEP* 2164.01). Furthermore, "it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these

factors, and any conclusion of nonenablement must be based on the evidence as a whole"' (*ibid.*, citing 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407).

In its rejection, the Office discussed the breadth of the claims, the nature of the invention, the state of the prior art, the level of predictability in the art, and the quantity of experimentation. Applicants note that the level of skill in the art at the time the invention was made was high as far as recombinant DNA analysis, but that the skill was relatively low in minichromosome production and use, wherein the minichromosomes contain plant-derived centromeres and are used to make adchromosomal plants.

Preliminarily, Applicants note that the claims have been amended, which amendments include recitations to specific polynucleotide sequences that confer centromere function; the recited polynucleotide sequences are supported by working examples, discussed below.

Firstly, regarding the Office's assertion that one needs all the listed elements to have an artificial chromosome, Applicants respectfully direct the Office's attention to page 2, lines 30-33, which teaches that artificial chromosomes may be linear or circular. In the case of circular artificial chromosomes, telomeres are not essential because there are no free ends to stabilize or termini to replicate.

Secondly, the Office described Bryant et al. (2001 *J. Experimental Botany* 52:193-202) as evidence that origins of replications are challenging to *isolate*. Applicants note that origins of replication can be integrated into artificial chromosomes by standard procedures known to one of skill in the art, such as a shot-gun approach using a functional assay; this isolation of a functional origin does not represent an undue amount of experimentation as it is well within the ability of one of skill in the art at the time the invention was made. In fact, whether there are specific defined origins of replication in higher eukaryotic cells is not clear – it may be that cells can use a wide variety of low-sequence specificity (A-T-rich DNA) as origins. Indeed, from practical experience in other systems, including mammalian artificial chromosomes, it appears that the cell will replicate any reasonably sized piece of DNA– in other words; it appears that one does not need to pro-actively build an origin into a minichromosome.

Thirdly, the application provides ample guidance to enable one to make minichromosomes having centromere repeats derived from any plant and to use such

minichromosomes to make the mini-chromosome-containing plants as claimed. The specification teaches how to identify centromere sequences (page 78, line 10 to page 80, line 6) and to assay those sequences for their ability to confer autonomy to a polynucleotide in cell division (page 80, line 7 to page 82, line 20). Furthermore, the specification teaches one of skill in the art how to construct minichromosomes by multiple examples, such as in Example 2 (starting at page 106), Example 7 (specifically at page 148, lines 1-7 and Table 28), Example 10 (page 160, lines 5-12), and Example 15 (starting at page 178). The specification also teaches across many plant genera that are evolutionarily distinct, exemplifying creating adchromosomal plants from minichromosomes having plant-derived centromeres, and analyzing the adchromosomal plants for the presence of the minichromosomes. These genera include dicots, such as *Brassica* (Examples 1-6, pages 100-143), tomato (Examples 7-9, pages 143-153), and soybean (Example 10, starting at page 153), as well as a monocot, corn (Examples 14-16, pages 163-182). The specification also exemplifies minichromosome analysis in adchromosomal plants in Example 11 (starting at page 163), including analysis of autonomy (Example 12, starting at page 166) and transmission of minichromosomes through meiosis (Example 13, starting on page 168).

In fact, the inventors went further than just to introduce plant minichromosomes into the same genera from which the centromere repeats were derived. For example, Example 9 discloses that the inventors created adchromosomal tobacco plants having minichromosomes with tomato centromere repeats, and that these minichromosomes were successfully introduced into tobacco plants; for example, see Table 38 on page 162, presenting PCR analysis for sequences unique to the introduced minichromosomes, and Table 47, page 172. Genes carried by the tomato-centromere repeat-based minichromosome were expressed in tobacco, as shown by the analysis of such a gene, a fluorescent marker analyzed in pollen, which data are presented in Tables 46 and 48 on pages 172-173. The Examples show that mini-chromosomes containing centromeres from one plant species, when inserted into plant cells of a different species or even a different genus or family, can be stable, functional and autonomous. For example, a broccoli centromere (*B. oleraceae*) is functional in a canola (*B. napus*) plant. Similarly, a tomato (*Lycopersicum*) centromere is functional in a tobacco

(*Nicotiana*) plant. A soybean (*G. max*) centromere is functional in broccoli (*B. oleraceae*) and tobacco. Tobacco and tomato are in the same family of Solanaceae; soybean is in the Leguminoseae family, and broccoli is in the Brassicaceae family – thus the inventors have demonstrated that adchromosomal plants comprising a functional, stable, autonomous mini-chromosome containing centromere sequence derived from a different taxonomic plant species, or derived from a different taxonomic plant species, genus, family, order or class, can be made.

The specification provides ample guidance to one of skill in the art to make and use minichromosomes having plant-derived centromeres to make adchromosomal plants across plant genera. Applicants note the diversity within the plant kingdom represented by the four plant species exemplified in the application, *Brassica oleracea*, *Glycine max*, *Zea mays* and *Lycopersicon esculentum* (plants of four different phylogenies, including three dicotyledonous plants and one monocotyledonous plant). The breadth of diversity is illustrated by the attached phylogenetic tree (**Exhibit A**). The specification discloses that the inventors have identified multiple functional centromere sequences for each of the exemplified species.

For these reasons, Applicants submit that the techniques disclosed in the specification enable the claimed invention and the enablement rejection may properly be withdrawn.

The rejection under 35 USC § 112, first paragraph for lack of written description should be withdrawn

The rejection of all pending claims under 35 USC §112, first paragraph, as allegedly failing to comply with the written description requirement should be withdrawn because a claimed genus is adequately described where one of skill in the art would be able to recognize the identity of members within the genus, and where there is a correlation between the structure of the invention and its function.

Preliminarily, Applicants note that the claims have been amended, which amendments include recitations to specific polynucleotide sequences that confer centromere function; the recited polynucleotide sequences are supported by working examples, discussed below.

Applicants respectfully traverse the rejection. The Office asserted that the claims are broadly drawn to a plant comprising a minichromosome constructed from any DNA content, from any species including animal, insect or fungal, or any crop plant species, wherein the host may be any species relative to the minichromosome species of origin. The Office believes that the claims represent "literally millions of embodiments and countless combination possibilities" (page 8 of the Office Action).

Applicants' amendment obviates the rejection because the claims are directed to centromeres comprising repeat nucleic acid sequences not from any species, but instead from a representative number of species, soybean, tomato and broccoli. The rejection may properly be withdrawn.

Rejection under 35 USC § 112, second paragraph (indefiniteness)

The Office rejected claim 6 under 35 USC 112, 2nd paragraph for being indefinite because claim 6 depended from a cancelled claim. Applicants have cancelled claim 6, obviating the rejection.

Objections to the specification

The Office objected to the specification because it contained embedded hyperlink code. Applicants have amended the specification to delete the offending material and added clarifying language to clarify the source of the information, making the objection moot. No new matter has been added as a result of Applicants' amendments. Applicants respectfully request the Office to withdraw its objections.

Objections to the Drawings

The Office objected to the Drawings (specifically, Figures 5 and 6) because they present nucleic acid sequences without listing corresponding SEQ ID NOs. The amendments to the Brief Description of the Figures of the specification address this objection by inserting sequence identification numbers that are referenced elsewhere in the specification. For example, the sequence identifiers for those sequences listed in Figure 5 are provided on page

20, lines 9-31, and for those sequences listed in Figure 6, on page 21, lines 1-11. These amendments do not add new matter to the specification.

Double-patenting (obviousness-type)

The Office has provisionally rejected the claims listed below on the grounds of non-statutory obviousness-type double patenting over the patents and patent applications listed below. Upon notice of an allowable claim and a maintaining of the double-patenting rejection, Applicants will either explain how the claims are patentably distinct, or will file a terminal disclaimer in the appropriate application.

1. The rejection of claims 1-3, 19, 25, 30, 40, 43-46, 54, 56-60, 66, 67, 76, 82, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1, 2, 6, 17-19, 21-24 and 25-27 of U.S. Patent No. 6,156,953.
2. The rejection of claims 1-3, 19, 25, 30, 40, 43-46, 66, 67, 76, 82, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-4 and 8-13 of U.S. Patent No. 6,900,012.
3. The rejection of claims 1-3, 10-11, 15-16, 19, 25, 30, 40, 43-46, 54, 56-58, 66, 67, 76, 82, 89, 90, 93 and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-38 of U.S. Patent No. 7,119,250.
4. The rejection of claims 1-3, 19, 25, 40, 43-46, 66, 67, 76, 82, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-16 of U.S. Patent No. 7,015,372.
5. The rejection of claims 1-3, 11, 15, 16, 19, 25, 30, 40, 43, 44, 46, 54, 56-58, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-7 of U.S. Patent No. 7,235,716.
6. The rejection of claims 1-3, 11, 15, 16, 19, 25, 30, 40, 43, 44, 46, 54, 56-58, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-7 of U.S. Patent No. 7,227,057.
7. The rejection of claims 1-3, 7, 10, 11, 14-16, 19, 25, 30, 40, 43, 44, 46, 54, 56-58, 66, 67, 76, 77, and 96 on the ground of non-statutory obviousness-type double

patenting over claims 1-22 of U.S. Patent No. 7,226,782.

8. The rejection of claims 1-3, 7, 10, 11, 14-16, 19, 25, 30, 40, 43-45, 54, 56-58, 76-77, 89-90, 93 and 96 on the ground of non-statutory obviousness-type double patenting over claims 1-22 of U.S. Patent No. 7,456,013.
9. The rejection of claims 1-3, 7, 11, 19, 25, 30, 39, 40, 43-46, 66, 67, and 96 on the ground of non-statutory obviousness-type double patenting over claims 128, 129, 132-145, and 150-152 of co-pending patent application no. 11/981,296.
10. The rejection of claims 1-3, 7, 11, 19, 25, 30, 39, 40, 43-46, 56-58, 66, 67, and 96 on the ground of non-statutory obviousness-type double patenting over claims 128-133 and 135-147 of co-pending patent application no. 11/981,451.
11. The rejection of claims 1-3, 19, 25, 30, 40, 43-46, 56-58, and 96 on the ground of non-statutory obviousness-type double patenting over claims 1, 2, 7, 8, 14, 18, 24, 30, 55, 56, and 59 of co-pending patent application no. 11/331,942.

CONCLUSION

In view of the foregoing, Applicant respectfully requests reconsideration and the timely allowance of the pending claims. Should the Office feel that there are any issues outstanding after consideration of the response; the Office is invited to contact the Applicant's undersigned representative to expedite prosecution.

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